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A STOCHASTIC MODEL FOR THE INTERPRETATION OF CLINICAL TRIALS

George H. Weiss and Marvin Zelen

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ABSTRACT

There are several diseases which can be characterized by the patient being in one of a finite number of states; e.g. relapse, remissive, toxic, etc. These states may be both transient and absorbing. Other authors have proposed similar models to describe data dealing with time dependent phenomena which have assumed that the distribution spent within any state is exponential. These models are all Markovian. In this paper we develop non-Markovian models which allow arbitrary distributions within a state. The model is applied to clinical trials of patients with acute leukemia who are undergoing experimental therapy. The agreement of the model and the data is very good.

A STOCHASTIC MODEL FOR THE INTERPRETATION OF CLINICAL TRIALS[1]

George H. Weiss[2] and Marvin Zelen[3]

1. Introduction

There are several diseases in which possibly recurrent phases may be distinguished. Different investigators have proposed Markovian models to describe data dealing with the time dependent phenomena associated with these diseases. We mention in particular the work of Fix and Neyman on cancer, [1], the work of Marshall and of Goldhamer on the epidemiology of mental disease, [2], and the work of Alling on tuberculosis, [3]. All of these assume that the distribution of time spent in an occurrence of a particular phase is negative exponential. In the following paper we present a semi-Markov model for data analysis, in which it is possible to consider any distribution for stay in a given phase. The theory has been applied to data on victims of both acute myelocitic and acute lymphocytic leukemia who have received experimental drug therapy. In our application we have found that gamma distributions give a convenient representation of the relevant probability densities. Hence any Markov theory will not be sufficient for the study of the statistics relating to leukemia. We feel

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[2] Institute of Fluid Dynamics and Applied Mathematics, University of Maryland and National Bureau of Standards.

[3] Mathematics Research Center, U. S. Army.

that the semi-Markov model presented here has wide applicability to many clinical situations.

The advantage of having a model is that it guides the investigator in the type and kinds of data to collect. Further a model serves as a convenient frame of reference for posing questions and suggesting further experiments. Too often the "effectiveness" of a treatment is measured by the "success-ratio". It is clear that other factors are also important; e.g. (using the terminology of the acute leukemia study), time in a remissive state, time to reach a remissive state, degree of toxicity, time to failure (if ailment is a fatal one), time to complete cure, etc.

2. Formulation of the Model

The health of a patient can be characterized at any instant of time by being in one of a finite number of states. In the clinical terminology, the patient may be in a relapse state, a remissive state, toxic state, etc. These remissive and relapse states may be further classified by the degree of remission or relapse and also by how many and kinds of relapse or remissions preceded the present state. In addition to these transient states, the patient may have entered a terminal (or absorbing, in the language of Markov processes) state such as failure, failure from other causes, cure, or patient lost.

We shall let T denote the set of transient states and A the set of absorbing states. Also we define

$U_i(t)$ = probability of being in state i at time t ;

$q_i(t)$ = probability density function for a single time in state $i \in T$;

$Q_i(t) = \int_t^\infty q_i(x)\,dx$

$\omega_i(t)\,dt$ = probability of leaving state i ($i \in T$) during the time interval $(t, t + dt)$;

p_{ij} = probability of passing from state i to j, conditional upon leaving i (by convention we set $p_{ii} = 0$ for $i \in T$).

It will be convenient to define the vector and matrix analogues of the above quantities. For this purpose we let

$\mathfrak{U}_T(t)$ = column vector of $U_i(t)$, $i \in T$

$\mathfrak{U}_A(t)$ = column vector of $U_i(t)$, $i \in A$

$\mathfrak{q}(t) = \left(\delta_{ij} q_i(t)\right)$ where δ_{ij} is the Kronecker delta

$\mathfrak{Q}(t) = \left(\delta_{ij} Q_i(t)\right)$

$\mathfrak{w}(t)$ = column vector of $\omega_i(t)$; $\mathfrak{U}^0 = (U_i(0)\,\delta_{ij})$, $i \in T$.

$$\mathfrak{P} = \begin{array}{c} \\ A \\ T \end{array} \begin{array}{c} \begin{array}{cc} A & T \end{array} \\ \begin{bmatrix} \mathfrak{L} & O \\ \mathfrak{R} & \bar{\mathfrak{P}} \end{bmatrix} \end{array}$$

As a further convention we denote the Laplace transform of any time dependent function by the same function with argument s and an asterisk; i.e. $\omega_i^*(s) = \int \{\omega_i(t)\}\, dt$, $\underset{\sim}{\omega}^*(s) = \int \{\underset{\sim}{\omega}(t)\}\, dt$.

Using familiar arguments in the theory of semi-Markov processes [4], one can obtain the following equations for $\underset{\sim}{\omega}^*(s)$ and $\underset{\sim}{U}_T^*(s)$:

$$\underset{\sim}{\omega}^*(s) = \underset{\sim}{q}^*(s)\underset{\sim}{U}^\circ + \underset{\sim}{q}^*(s)\bar{\underset{\sim}{P}}'\underset{\sim}{\omega}^*(s) \tag{1}$$

$$\underset{\sim}{U}_T^*(s) = \underset{\sim}{Q}^*(s)\underset{\sim}{U}^\circ + \underset{\sim}{Q}^*(s)\bar{\underset{\sim}{P}}'\underset{\sim}{\omega}^*(s) \tag{2}$$

which yield the solutions

$$\underset{\sim}{\omega}^*(s) = [\underset{\sim}{I} - \underset{\sim}{q}^*(s)\bar{\underset{\sim}{P}}']^{-1}\underset{\sim}{q}^*(s)\underset{\sim}{U}^\circ \tag{3}$$

$$\underset{\sim}{U}_T^*(s) = \underset{\sim}{Q}^*(s)[\underset{\sim}{I} - \bar{\underset{\sim}{P}}'\underset{\sim}{q}^*(s)]^{-1}\underset{\sim}{U}^\circ \quad . \tag{4}$$

Let $U_A(t)$ denote the probability of being in an absorbing state at time t. Then we have

$$U_A^*(s) = \frac{1}{s} - \sum_{i \in T} U_i^*(s) \tag{5}$$

from which the moments of the time to reach absorption can easily be calculated by noting that the Laplace transform of the survivorship function; i.e. $G(t) = \text{Pr.}\{\text{failure time} > t\}$ is

$$G^*(s) = \sum_{i \in T} U_i^*(s) = \underset{\sim}{1}' \underset{\sim}{U}_T^*(s) \tag{6}$$

where $\underset{\sim}{1}$ is a column vector of appropriate dimension having all elements unity.

For the purpose of writing the moments associated with $G(t)$, define

$$m_i(k) = \int_0^\infty t^k q_i(t)\,dt, \qquad \underset{\sim}{M}(k) = \left(m_i(k)\,\delta_{ij}\right)$$

$$\underset{\sim}{\tau} = \lim_{s \to 0+} \underset{\sim}{\omega}^*(s) = (\underset{\sim}{I} - \bar{\underset{\sim}{P}}')^{-1} \underset{\sim}{U}^0 \quad .$$

Note that τ_i is the expected number of times state i is visited. Then the mean and variance of the time to reach absorption are

$$E(t) = \lim_{s \to 0+} G^*(s) = \underset{\sim}{1}' \underset{\sim}{M}(1)[\underset{\sim}{I} - \bar{\underset{\sim}{P}}']^{-1} \underset{\sim}{U}^0 = \underset{\sim}{1}' \underset{\sim}{M}(1) \underset{\sim}{\tau} \tag{7}$$

$$\sigma^2 = -\lim_{s \to 0+} \{2\frac{dG^*(s)}{ds} + [G^*(s)]^2\} = \underset{\sim}{1}' \underset{\sim}{\Sigma} \underset{\sim}{\tau} + \underset{\sim}{1}' \underset{\sim}{M}(1)\left\{[2(\underset{\sim}{I} - \bar{\underset{\sim}{P}}')^{-1} - \underset{\sim}{I} - \underset{\sim}{\tau}\underset{\sim}{1}'] \underset{\sim}{D}(\tau)\right\} \underset{\sim}{M}(1)\,\underset{\sim}{1} \tag{8}$$

where

$$\underset{\sim}{\Sigma} = \underset{\sim}{M}(2) - \underset{\sim}{M}^2(1)$$

$$\underset{\sim}{D}(\tau) = \begin{pmatrix} \tau_1 & & 0 \\ & \tau_2 & \\ & & \ddots \\ 0 & & \tau_n \end{pmatrix} \tag{9}$$

Relatively simple recursive relations can be derived for the higher moments.

In addition to the results given so far, it is possible to develop a theory in which the p.d.f. $q_i(t)$ is replaced by $q_{ij}(t)$, i.e., in which the time spent in any state depends either on the succeeding or the following state. However, the results do not have the simplicity of those of Equations (7) and (8). They will appear in a forthcoming publication. Another statistic of some interest in drug evaluation is the total time spent in a given transient state. This is important in the leukemia study, since it is desirable to prolong a patient's life in a condition of remission rather than in a condition of active illness. Let us consider a single remissive state i and partition the transition matrix $\underset{\sim}{P}$ as

$$\underset{\sim}{P} = \begin{array}{c} \begin{matrix} A & i & T-i \end{matrix} \\ \begin{bmatrix} \underset{\sim}{\lambda} & \underset{\sim}{\alpha} & \underset{\sim}{\alpha} \\ \underset{\sim}{\delta} & \underset{\sim}{\alpha} & \underset{\sim}{\beta} \\ \underset{\sim}{\gamma} & \underset{\sim}{\alpha} & \underset{\sim}{\Pi} \end{bmatrix} \begin{matrix} A \\ i \\ T-i \end{matrix} \end{array} \quad . \tag{10}$$

Then the probability of entering state i at least once starting from state j is

$$\begin{aligned} h_{ji} &= [(\underset{\sim}{I} - \underset{\sim}{\Pi})^{-1} \underset{\sim}{\alpha}]_j \qquad j \neq i \\ h_{ii} &= \underset{\sim}{\beta}\, \underset{\sim}{\Pi}\, (\underset{\sim}{I} - \underset{\sim}{\Pi})^{-1} \underset{\sim}{\alpha} \quad . \end{aligned} \tag{11}$$

The first two moments of the total sojourn time in state i conditional on

starting from state j are

$$\left.\begin{aligned} \mu_{ji}(1) &= \frac{m_i(1)}{1-h_{ii}}\,\delta_{ij} + \frac{m_i(1)h_{ji}}{1-h_{ii}}\,(1-\delta_{ij}) \\ \mu_{ji}(2) &= \left[\frac{m_i(2)}{1-h_{ii}} + \frac{2m_i^2(1)h_{ii}}{(1-h_{ii})^2}\right]\left[\delta_{ij} + h_{ji}(1-\delta_{ij})\right] \quad . \end{aligned}\right\} \tag{12}$$

3. Applications to Acute Leukemia Clinical Data

A large number of clinical trials were conducted by the Acute Leukemia Group B (Frei et al. [5]) on patients having acute leukemia. In this section we will illustrate the application of our model to a portion of these data. A more complete discussion of the data will be given in another publication.

All patients entered these clinical trials while in a state of relapse. The data examined in this paper were for patients who were initially given Methotrexate (MTX). The patients either never responded and expired, or eventually reached a remissive state. A distinction was made between a partial and complete remission. If the patients did not show remission within the first 6 weeks, the MTX therapy was stopped, a period of two weeks was allowed to elapse, at the conclusion of which the surviving patients who were still in a state of relapse were given 6-mercaptopurine (6-MP). Further, if a patient who was in remission entered a relapsed state, the therapy was changed to the alternate drug (MTX or 6-MP).

In this paper we will apply the model to date from 26 patients who achieved a state of remission within 8 weeks of entering these clinical trials. In our application we will be mainly interested in the distribution of the time to failure. Since, by definition, a remissive state is always followed by a relapse state we will combine the sojourn time in a relapse state with the sojourn time of the remissive state which immediately preceded it. Another characteristic of this application is that the data indicate different sojourn time distributions which depend on the number of times the patient has been in the state. With these characteristics of the process in mind, we define the six states:

S_0 : failure (death)

S_1 : initial relapse state (condition of patient on entering study)

S_2 : first partial remission (also includes subsequent relapse)

S_3 : second partial remission (includes subsequent relapse)

S_4 : first complete remission (includes subsequent relapse)

S_5 : second complete remission (includes subsequent relapse)

The communication among states may be summarized in the following diagram where all states connect with S_0.

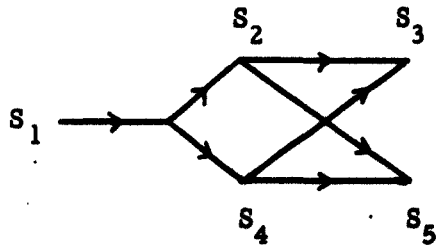


Figure 1

State Diagram for a Model of Leukemia

An investigation of the distribution of sojourn times within the various transient states showed that with the exception of the initial state, these distributions can be well approximated by gamma distributions, i.e.

$$\varphi(t) = \lambda e^{-\lambda t}(\lambda t)^{a-1}/\Gamma(a), \quad t \geq 0, \quad a > 0 .$$

The parameters (a, λ) were estimated from the data by the method of maximum likelihood with the aid of the convenient tables of Wilk, Gnanadesikan, and Huyett [6]. Table 1 summarizes the results of these calculations.

Table 1

Sample Means, Variances, and Maximum Likelihood Estimates of the Parameters of Gamma Distribution*

State	$\hat{a}$	$\hat{\lambda}$	$\hat{m}(1)$	$\hat{\sigma}^2$	Sample Size
S_2 (first P.R.)	2.3	0.101	23.1	189	14
S_3 (second P.R.)	2.9	.122	23.6	215	7
S_4 (first C.R.)	4.7	.132	35.6	310	27
S_5 (second C.R.)	15.5	.463	33.6	90	7

It remains to obtain estimates of the transition probabilities $\mathcal{P}$ before the formulas of the preceeding section can be applied. The observed relative frequencies (conditional on going to a remission state) observed in these clinical trials were used as estimates of the (p_{ij}). The numerical results are:

$$\mathcal{P} = \begin{array}{c} \\ S_0 \\ S_1 \\ S_2 \\ S_3 \\ S_4 \\ S_5 \end{array} \begin{array}{c} \begin{array}{cccccc} S_0 & S_1 & S_2 & S_3 & S_4 & S_5 \end{array} \\ \left[\begin{array}{c|cccccc} 1 & 0 & 0 & 0 & 0 & 0 \\ \hline 0 & 0 & 10/26 & 0 & 16/26 & 0 \\ 5/10 & 0 & 0 & 3/10 & 0 & 2/10 \\ 1 & 0 & 0 & 0 & 0 & 0 \\ 9/16 & 0 & 0 & 4/16 & 0 & 3/16 \\ 1 & 0 & 0 & 0 & 0 & 0 \end{array}\right] \end{array}$$

* These estimates are based on all patients who went into a remission state regardless of whether they left the initial relapse state within eight weeks or after.

The estimate of the transition matrix $\mathcal{P}$ and the parameters of the gamma distribution summarize the relevant information with the exception of the sojourn time distribution for the initial relapse state (S_1). Here the distribution is complicated by being truncated at the end of eight weeks. Since the data are summarized in units of a week, this distribution (conditional on a patient reaching a remissive state) was assumed to be a discrete distribution where p_n denotes the probability of entering a remissive state after n weeks in the initial relapse state. The observed relative frequencies were taken as the estimates for p_n and were:

$$n = \quad 2 \quad 3 \quad 4 \quad 5 \quad 6 \quad 7$$

$$p_n = [2/26 \quad 6/26 \quad 8/26 \quad 5/26 \quad 4/26 \quad 1/26]$$

A check on the model can be obtained by comparing the sample mean and variance of the time to reach failure with the theoretical formulas given in (7) and (8). The numerical results are:

	Data	Model
Mean	48.4	49.7
Variance	515.	525.

We now turn our attention to estimating the distribution of the time to reach the failure state. The probability density function for those patients

reaching a remissive state can be calculated using (6). After some reduction, the result is:

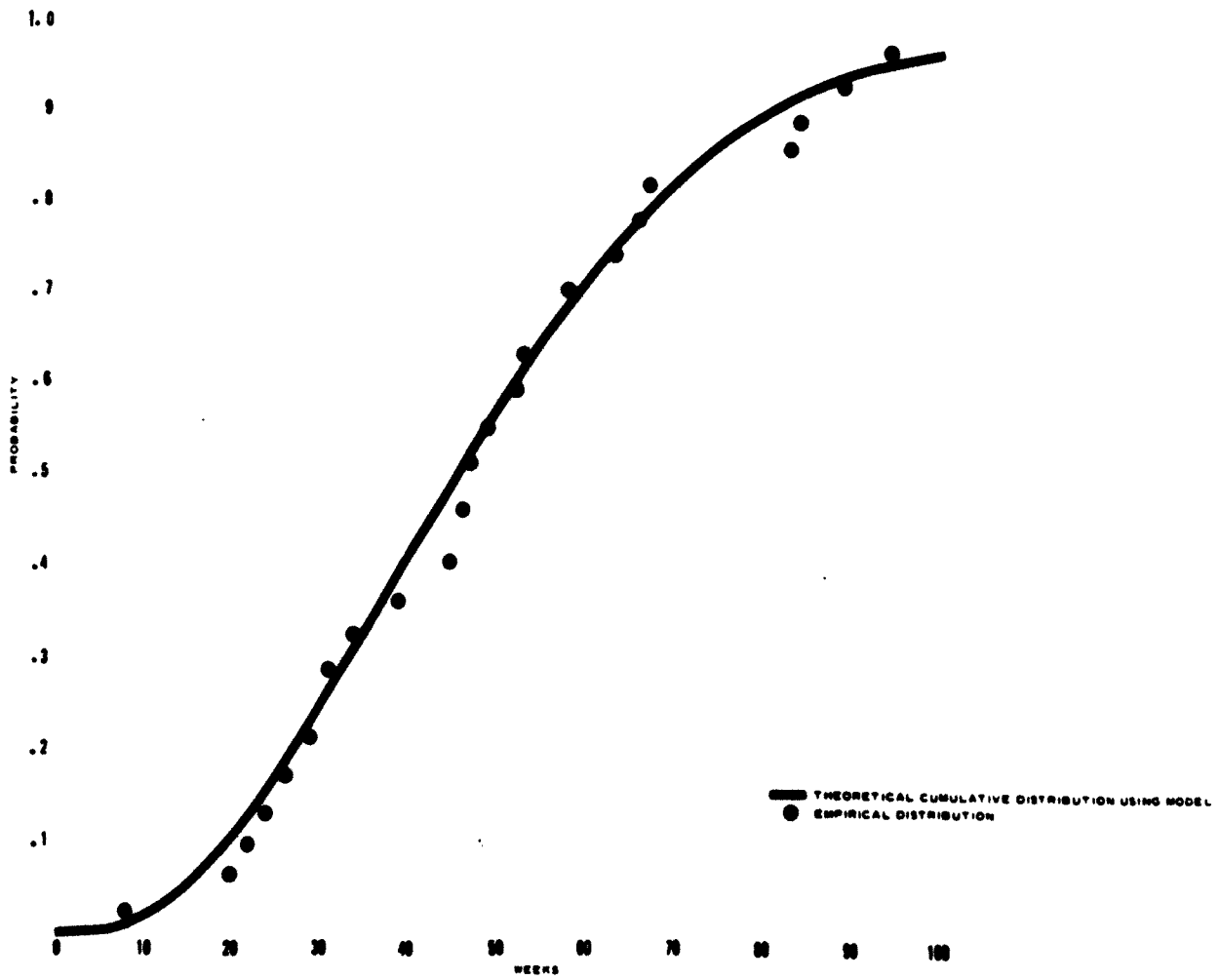
$$g_0(t) = p_{20}p_{12}[\varphi_1 * \varphi_2] + p_{30}[p_{12}p_{23}(\varphi_1 * \varphi_2 * \varphi_3) + p_{14}p_{43}(\varphi_1 * \varphi_3 * \varphi_4)]$$

$$+ p_{40}p_{14}[\varphi_1 * \varphi_4] + p_{50}[p_{12}p_{25}(\varphi_1 * \varphi_2 * \varphi_5) + p_{14}p_{45}(\varphi_1 * \varphi_4 * \varphi_5)]$$

(The notation $\varphi_1 * \varphi_2$ denotes the convolution of $\varphi_1(t)$ and $\varphi_2(t)$, where $\varphi_1(t)$ denotes the frequency function of the initial relapse state.)

Note that $g_0(t)$ is made up of a mixture of distributions which involve convolutions of gamma distributions. For our purposes, the approximation of convolutions of gamma distributions by a gamma distribution with the same first two moments was deemed a sufficient approximation. Figure 2 contains a plot of $G_0(t) = \int_0^t g_0(x)\,dx$ along with the sample data. The agreement is remarkable.

We would like to thank Dr. Edmund Gehan of the National Institutes of Health for helpful discussions of this problem and his cooperation in providing us with records of the leukemia study.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WEEKS
THEORETICAL CUMULATIVE DISTRIBUTION USING MODEL
EMPIRICAL DISTRIBUTION

Figure 2

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